Calibration & Validation Group

Mission: To partner with industrial, academic and regulatory bodies to provide education and forums for discussion of calibration and validation practices throughout the nation

November 22, 2000

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane
Rm. 1061
Rockville, MD 20852

Re: (Docket No. 00D-1424) Draft Guidance for Industry on Analytical Procedures and Methods Validation: Chemistry, Manufacturing, and Controls Documentation

The Calibration & Validation Group (CVG) is pleased to have the opportunity to comment on the draft guidance. CVG is a non-profit discussion group formed by over 800 scientists from the pharmaceutical industry, chemical industry, academia and government agencies in Canada. Our objectives include promotion of instrument calibration and method validation in the laboratory and to increase awareness of cGMP's/GLP's. We would like to thank FDA for providing guidance with respect to analytical procedures validation.

To further assist the FDA in the development of the draft guidance, we have organized a Workshop to discuss this guidance document on October 23. We are attaching the summary of the comments with rationale on a line by line basis for the draft guidance issued August 2000. If you have any question, please do not hesitate to contact me at (416)693-3724.

Thank you.

Yours sincerely,

Chung Chow Chan, Ph.D.
President, CVG

00D-1424

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CVG Workshop on FDA Guidance for Analytical Procedures and Methods Validation October 23 2000

line Number	Section	Comments	Proposals
Title		Wording of title	Define "analytical procedures" and "methods" in glossary. Are methods and analytical procedures different?
120-130	III	By definition, "stability indicating" should only need to examine degradation products and will not include process impurities, excipients, etc	Line 124-125 will read: "...measures active ingredients, without interference from degradation products and process impurities. Excipients, or other potential impurities will be assayed as desired".
137	IV	Other official sources of Reference Standards?	Need a complete list of other official reference standards.
149	IV	"...ensure **suitability** of the reference standard." What does this mean? Possible example of suitability: free base vs. HCl salt. Fine for potency test but not for ID.	".....the user should ensure the suitability of the reference standard if used for something other than its intended use."
Sections V and VI		Contents do not flow well in this order.	Section VII should come immediately after Section V. Section XI should come immediately after Section VI.
237	VI	Are there other examples of acceptable methods sources other than AOAC?	Include a full list of other method sources in an Appendix.
246-249	VI	More detail description of what is expected of the method and why.	Elaborate on the principles e.g. is it for potency, impurities, etc.
251	VI	Need to be precise on the samples.	USP gives exact numbers of how many tablets are required for certain tests. This document is unclear concerning the analysis procedure e.g. 3 injections from one sample or 3 different samples from the original composite.
251-255	VI	More information of sampling is required in this section.	The sample should reflect the true composition of the batch to avoid bias.
321-345	VI	Impurities recommendation is not similar to ICH suggestions. "Total impurities" penalized groups with very low quantitation limit.	Line 331 (#3) should read "any unspecified impurities at or above their QL".
323	VI	Remove retention time (RT) as location/ID for impurities. Retention times can change with dwell volume and is not appropriate for cross chromatogram comparisons for ID.	Remove RT as option. RRT is more appropriate.
441-443	VII	"drug substance" and "active ingredient" used interchangeably throughout document. It will be better to stay with one consistent	In this case replace with "...photolysis, oxidation) for the drug substance and drug substance in the formulation

		terminology.	should be provided..."
444	VII	Delete the whole sentence. Previous sentence with "demonstrate specificity" is redundant to sentence in line 444 with "...do not interfere with quantitation of the active"	Delete the whole sentence: "The stress studies that should demonstrate.....do not interfere with the quantitation of the active ingredient".
723	X	"Sample of impurities" need to be defined.	Major named impurities or major named degradation products to replace "sample of impurities".
	XI(F) and VI(B)	There is a lack of sampling requirements for particle size. Sampling should be representative of batch and do not introduce bias. This is important and to be mentioned up front.	A note should be added to include sampling specifically for particle size analyzer.
	XI	Add in a section on wet chemistry analysis e.g. Titration or Karl Fisher.	KF is an important attribute of pharmaceutical analysis and should be included. Include this in Section XI under "Titration techniques". This section will complement the existing section in USP.
821	XI	Replace the word 'plastic' with 'polymer'.	More scientific expression.
823	XI	"Frit size" is not a useful column parameter.	Remove "frit size" from list of column parameters.
846	XI	Capacity factor is difficult to determine and not accurate & useful.	Remove capacity factor.
866-871	XI	The type of mixing can adversely affect HPLC runs with a mobile phase gradient.	Add sentence regarding possibility of additional parameters being examined e.g. low or high pressure mixing during mobile phase gradient.
973	XI	Optical rotation is not sufficiently sensitive for measuring enantiomeric purity of compounds with small optical rotation. The method is generally useful for establishing enantiomeric identity.	Replace 1st sentence with "Optical rotation is used for establishing enantiomeric identity and may be used for measuring enantiomeric purity".
998-1035	XI	Not listing the operating parameters of particle analyzer	List the model made of the instrument as the analyses of particle size are instrument specific.
998, 1000, 1005, 1009 and 1011	XI (F)	There are many characteristic studied than just 'particle size' alone	Replace title in line 998 of "Methodologies Relating to .Particle Size Analysis" with "Methodologies Relating to Particle Characterization'.
1026	XI	Size exclusion chromatography. It does not really belong as it is more of a 'molecular study'.	Remove "size exclusion chromatography".
1066	XI	The validation of the dissolution	Define dissolution procedures

		technique need to be differentiated from the validation of the analysis of the samples.	e.g. paddle vs. basket, medium used, or rpm. Clearly define components of dissolution procedure that need validation, **or alternatively**, Change the sentence to read "Dissolution procedure should be justified and the method of analysis should be validated".
1108-9, 1115, 1118	Attachment A	Reference is not correct	1108: Section VII.A 2.**b** not c 1109: Section VII.A.2.**c** not b. 1115: Should be Section **X**
1108, 1116 and 1122	Attachment A	Reduce duplication of stress study information in different places of the submission.	Consolidate a section on Stress Study e.g. 'Degradation Information from Stress Studies' in the submission document.

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